specification, specifically, for example, at page 6, line 3 though page 7, line 3. No new matter is added by these amendments, and entry of the same is respectfully requested.

Rejections Under 35 U.S.C. § 102

On page 6 of Paper No. 20, the Examiner rejects claims 1-3, 10-13, 24, 25, and 27 under 35 U.S.C. § 102(b) as "anticipated by *Mason et al* (J Virol 1980; 36:829-36) and as evidenced by *Birkett* (US 6,231,864)." Applicants respectfully traverse this rejection.

The present claims relate to an elegant platform useful in stimulating an immune response against a myriad of disease conditions. The platform is based on recombinant duck hepatitis B core protein (duck HBcAg), which provides several advantages over other immunogenic protein carriers. For instance, duck HBcAg will not cross-react with tests for human HBcAg, so that blood supplies may still be tested for human HBV contamination even if individuals have been vaccinated with a duck HBcAg-containing vaccine. Furthermore, because duck HBV is not a pathogen in humans, it is possible that immune response can still be stimulated in individuals already infected with human HBV using the duck HBV platform. Moreover, the recombinant nature of the present inventions allows for one or more haptens to be introduced into the duck HBcAg monomer sequence, such that haptens can be introduced directly and easily into the vaccine platform. Additionally, recombinant duck HBcAg monomers may be produced in a variety of host cell cultures, alleviating the need for infected ducks, and the monomers can be purified easily and assembled into particles. Indeed, these particles can be disassembled and reassembled under mild conditions, allowing for a great variety of monomer- and/or monomer-hapten-particles. Such particles may include different haptens, from pathogens and/or cancers, allowing for a single vaccine offering protection against one or more diseases. Finally, the ease with which these particles may be disassembled and reassembled, under mild conditions, offers advantages over other HBV particles that require comparatively harsh conditions for their preparation and use.

In order to support an anticipation rejection under 35 U.S.C. § 102, the burden is on the USPTO to demonstrate that each and every element of a claimed invention has been disclosed or is inherent within a single prior art reference. *See, e.g., In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990). Importantly, the publication must describe an applicant's claimed invention sufficiently to have placed a person of ordinary skill in the art in the field of the invention in possession of it at the time the application was filed. *See generally In re Paulson,* 31 U.S.P.Q.2d 1671 (Fed. Cir. 1994). The reference must put the

anticipating subject matter into the possession of the public though an enabling disclosure. *Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1136 n.2 (Fed. Cir. 1990). Moreover, as the Federal Circuit has instructed, "[t]he mere fact that a certain thing may result from a given set of circumstances is insufficient to prove anticipation." *Electro Medical Systems, S.A., v. Cooper Life Sciences Inc.*, 32 U.S.P.Q.2d 1017, 1020 (Fed. Cir. 1994).

Mason does not provide adequate grounds to support a § 102(b) rejection, and Birkett does not remedy Mason's deficiencies. Birkett, used in conjunction with Mason, is used improperly in the context of this anticipation rejection, because each and every element of the claimed inventions must be found in a *single* reference. The rejection should be withdrawn for this reason alone.

Regarding Mason, the Examiner asserts that "*Mason et al* disclose native duck HBcAg particles comprising at least two different haptens present on the same or different nucleocapsid monomers ...." Paper No. 20 at page 7. Mason, however, does not disclose each and every element of amended claim 1, and did not place the composition of the claims in possession of a person of ordinary skill in the art at the time the pending application was filed. Specifically, although Mason refers to a newly discovered HBV-like virus, Mason does not mention, much less enable, a recombinant form of any of the proteins of this virus, much less a recombinant nucleocapsid monomer. Nor does Mason hint at how such recombinant monomers could be made and assembled into a particle. Indeed, although the Examiner notes that the instant specification teaches that the claimed recombinant particles may have sequences identical to native duck sequences (Paper No. 20 at page 7), Mason provides no sequence information whatsoever.

Furthermore, Mason is completely silent regarding haptens, antigens, and the like. Mason conducted several DNA hybridisation and electron microscopy analyses, but never studied the antigenic nature of the viral particles and never identified a single antigen from this virus, much less HBcAg. Clearly, Mason did not refer to a recombinant HBcAb that is linked to a non-HBV hapten as recited in claim 24.

Regarding Birkett, this patent issued on 15 May 2001, more than two years after the priority date on which the instant application relies. Hence, Birkett is not available as a prior art reference to bolster a § 102(b) inherency rejection based on the 1980 Mason. Moreover, extrinsic evidence such as Birkett may be used to explain, but not expand, the meaning of a reference. *In re Baxter Travenol Labs*, 21 U.S.P.Q.2d 1281, 1284 (Fed. Cir. 1991). Clearly, the Examiner is using Birkett in an improper way to expand the meaning of Mason, as

summarized above. Birkett is further deficient for a variety of reasons as explained further below.

Similarly, on page 7 of Paper No. 20, the Examiner suggests that Schödel supports Mason. Schödel, however, never once mentions the word "duck," so this reference clearly does not support an inherency rejection to claims limited to duck hepatitis virus-derived particles. Moreover, as described in greater detail below, Schödel does not describe assembled particles that include a portion of monomers that include a non-HBV hapten. In conclusion, these references do not support a § 102(b) rejection over the amended claims, and Applicants respectfully request that this § 102(b) rejection be reconsidered and withdrawn.

On page 7 of Paper No. 20, the Examiner rejects claims 1, 2 and 10 under 35 U.S.C. § 102(b) as "anticipated by *Yang et al* (J Virol 1994;68:338-45)." Applicants traverse the rejection.

Yang does not teach each and every element of the claimed inventions. Although Yang refers to constructs of recombinant HBcAg monomers that may or may not assemble in *E. coli*, Yang refers only to the antigenicity of the monomers in relation to DHBV polyclonal sera. As the Examiner noted, in particular, Yang's particle "comprises at least one hapten of DHBV core antigen associated with duck hepatitis infection." Paper No. 20 at pages 7-8. Yang does not, however, refer to an antigenic non-HBV hapten that may be included within such monomers. Claims 1 and 10, as amended, now clarify that the hapten of the present inventions is an antigenic non-HBV hapten. Because this limitation is not disclosed in Yang, Yang does not support a § 102 rejection. Hence, Applicants respectfully request that this rejection be withdrawn.

Next, the Examiner rejects claims 1-3, 10-13, 24, 25 and 27 under 35 U.S.C. § 102(b) as "anticipated by *JP 07252300*. (10/3/95)." Paper No. 20 at page 8. Applicants traverse the rejection.

Specifically, the Examiner notes that this paper refers to "fusion proteins (recombinant) between duck HBcAg and human HBV comprising at least two different immunogenic haptens, the duck core antigen and various human HBV antigens . . . which are associated with hepatitis infection in the human and duck." Paper No. 20 at page 8. The JP publication, however, does not appear to refer to non-HBV constructs. The amended claims relate to antigenic non-HBV hapten constructs that are not taught or suggested in the JP

reference. Hence, this reference does not support a § 102 rejection because it fails to teach each and every element of the claimed inventions. The Examiner is invited to provide the Applicants with a full translation of this reference if she does not agree with Applicants' interpretation of same. Applicants request that this § 102 rejection be withdrawn.

Thereafter, the Examiner rejects claims 1-3, 10-13, 24, 25 and 27 under 35 U.S.C. § 102(b) as "anticipated by *Weizacker et al* (Hepatol 1996; 24-294-99)." Paper No. 20 at page 8. Applicants traverse the rejection.

Weizacker refers to various duck HBV core protein constructs that were made to gauge interference in the viral replication and encapsidation process. Weizacker's work was limited (with the exception of GFP and lacZ constructs, both non-hapten marker proteins) to HBV constructs (either surface or polymerase coding sequences). In that regard, Applicants disagree strongly with the Examiner's statement that Weizacker teaches "at least a 1st hapten, intrinsic or extrinsic mosaic." Paper No. 20 at page 8. Indeed, Weizacker relates neither to antigenic constructs, nor the present claims drawn to non-HBV antigenic hapten constructs. Additionally, the Examiner asserts that "core and surface antigens are associated with hepatitis infection; thus, *Weizacker et al* anticipate the instant claims." *Id.* Applicants urge that the instant claims are not drawn to hepatitis infection. Thus, as Weizacker does not teach each and every element of the claimed inventions, Applicants request that this § 102 rejection be withdrawn.

On page 8 of Paper No. 20, the Examiner rejects claims 1-3, 10-13, 24, 25 and 27 under 35 U.S.C. § 102(e) as "anticipated by *Birkett et al* (US 6,231,864)." Applicants traverse the rejection.

Birkett refers to a vaccine approach using human hepatitis B, stating "'hepatitis B' as used herein, refers in its broadest context to any member of the family hepadnaviridae, a family of enveloped DNA-containing animal viruses that can cause hepatitis B *in human*." U.S. Patent No. 6,231,864 B1 at col. 7, lines 30-33 (emphasis added). The Examiner cites column 3 regarding self-assembly, but this portion of Birkett relates to studies related to human viruses only, is unclear whether it relates to recombinant human viruses, and does not explain how one would make recombinant duck monomers that are assembled to form particles. *Id.* at col. 3, lines 14-24. A closer reading of Birkett clarifies that this patent refers to human, and not duck, HBV. For example, the patent states, at col. 3, lines 46-53, that

Birkett's HBV core protein contains four cysteine residues. In contrast, as taught by the present application at page 21, lines 7-11, duck core protein has but one cysteine residue. Therefore, Birkett is not drawn to recombinant duck HBV core particles as are the pending claims.

As the Examiner notes on Page 9 of Paper No. 20, "*Birkett* teaches a composition comprising a modified HBV core protein or its aggregated nucleocapsid protein particles, *pendently linked* to a hapten." (emphasis added.) In Birkett, "pendently linked" "is used to describe the linkage between a hapten and a chemically-reactive amino acid side chain of a strategically modified hepatitis B core protein." *See* Birkett at col. 8, lines 13-19. Birkett generated a particle in which all monomers were modified to include a reactive amino acid sequence. A hapten might then be chemically linked to this reactive sequence, but was not otherwise included in the monomer. *Id.* at col. 11, lines 7-12; Examples 2 and 3; cols. 26-27. Birkett does not refer to assembling a particle of recombinant monomers to form a particle in which a portion of the recombinant monomers includes a hapten.

Although Birkett refers, in general, to the notion that an epitope could serve as the reactive amino acid linkage point for the hapten, as the Examiner asserts on page 9 of Paper No. 20, Applicants ask the Examiner to point out where Birkett enables such a feat, as is the burden of the USPTO under § 102. *See generally In re Paulson,* 31 U.S.P.Q.2d 1671 (Fed. Cir. 1994); *Chester v. Miller*, 15 U.S.P.Q.2d 1333 (Fed. Cir. 1990). Indeed, it appears that Birkett allegedly teaches only the insertion of lysine linkage points, to which various synthetic peptides derived from human cytochrome P450 enzymes were conjugated chemically. Birkett at Examples 1-4. In fact, the antigenicity (the very foundation of a hapten) of such constructs is never taught or suggested. Similarly, although Birkett refers, in general, to particles made of modified subunits, some of which have been successfully conjugated to a hapten, Applicants do not see where Birkett refers to a single particle that has a mixture of haptens. In that regard, as before, the Examiner must indicate where Birkett enables the assembly of such a particle. Such a particle would include, not reactive amino acids for chemical linkage, but haptens themselves, and would require the assembly of such particle from its monomer constituents. Otherwise, Birkett fails to teach every element of the pending claims, and Applicants request that this rejection under § 102 be reconsidered and withdrawn.

On page 9 of Paper No. 20, the Examiner rejects claims 1, 2, and 10 under 35 U.S.C. § 102(a) as "anticipated by *Kock et al* (J Virol 1998;72:9116-20)." Applicants traverse the rejection. Köck was made available to the public in October of 1998, as evidenced by the date-received stamp on the cover of the journal containing the article, a copy of which is attached to the Declaration of Darrell L. Peterson, Ph.D., Under 37 C.F.R. § 1.131, filed concurrently herewith. Dr. Peterson avers that he conceived the presently claimed inventions prior to the public availability of Köck and thereafter diligently reduced the presently claimed inventions to practice. Hence, Köck is no longer applicable as a § 102(a) publication. Applicants thus request that this § 102(a) rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

Finally, on page 10 of Paper No. 20, the Examiner rejects claims 1-3, 10, 11, 13, 24, 25 and 27 under 35 U.S.C. § 103(a) as "being unpatentable over *Schodel et al* (J Biotechnol 1996;44:91-6), in view of *Birkett* (US 6,231,864)." Applicants traverse the rejection. Applicants note that the PTO has the burden to establish a *prima facie* case of obviousness and to establish, in particular, that the cited references motivate one of ordinary skill in the art to achieve the claimed inventions by providing a reasonable expectation of success regarding the claimed subject matter. The use of hindsight is improper in making a *prima facie* case. *See generally In re Vaeck,* 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Examiner admits that Schödel does not "teach the duck HBV." Paper No. 20 at page 10. In fact, Schödel never mentions any species of HBV other than the human form with which he worked. More importantly, Schödel teaches away from the present inventions by suggesting that the way to reduce the level of anti-human HBc antibodies (linked to suppression of the immune response and the inability to screen blood for HBV infection) is to remove the antigenic sites of the human HBcAg. Schödel at page 93, col. 1. Schödel clearly does not suggest using duck HBV, which does not cross-react with human HBcAg antibodies, to overcome these problems. Indeed, this is a major advantage of the claimed inventions over Schödel.

Furthermore, this reference does not teach or suggest that, or how, recombinant duck HBcAg monomers may be assembled into a particle that may then be disassembled and reassembled. Instead, Schödel allegedly made particles of one kind of monomer from one host, one at a time. Schödel did not generate two populations of monomers, some of which contained a foreign hapten, and form particles from those populations of monomers. Note,

for example, the paragraph of Schödel bridging page 93, col. 2 and page 94, col. 1. In fact, Schödel does not mention how his constructs might be disassembled and reassembled to create the particle of the pending claims. Indeed, human HBcAg monomers require harsh conditions to disassemble the particles. In contrast, as taught by the present application at page 21, lines 7-11, duck HBcAg particles can be disassembled and assembled under mild conditions. The present inventions allow flexibility in packaging the hapten of choice; clearly, the claimed inventions are elegant systems far superior to the system allegedly taught by Schödel.

Moreover, Schödel reports that his human HBcAg-malaria antigen particles failed to elicit a T-cell response. Schödel at page 95, col. 2. Applicants have noted, at pages 1-3 and within Examples 1 and 2 of the instant application, that this is an important advantage of the inventions reflected in the pending claims. Hence, Schödel does not provide any motivation or expectation of success for creating the monomers and particle of the pending claims as required to establish a *prima facie* case of obviousness.

Birkett fails to remedy the deficiencies of Schödel. To summarize, Birkett proposes a completely different approach to creating a human HBV particle: the chemical conjugation of haptens to a uniform population of modified HBV monomers. In that regard, Birkett teaches away from the instant claims referring to recombinant monomers, a portion of which include at least one hapten. Moreover, although Birkett refers in passing to duck HBV, Birkett presents no suggestion or motivation to use duck HBV as opposed to woodchuck, squirrel, or any HBV other than the human HBV of Birkett. Further, Birkett provides no information, much less the motivation or expectation of success, related to the disassembly and reassembly of the particles required to create the particle of the instant claims. Hence, Birkett does not support a § 103 rejection based on Schödel. Applicants therefore request that the § 103 rejection be reconsidered and withdrawn.

CONCLUSION

For the foregoing reasons, Applicants submit that all of the pending claims are in condition for allowance. Applicants respectfully request reexamination of the present application, reconsideration and withdrawal of the present rejections, and entry of the amendments. Should there be any further matter requiring consideration, the Examiner is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present communication, please charge the fees to the undersigned's Deposit Account No. 50-1067. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to the undersigned's deposit account.

Respectfully submitted,

20 December 2002

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Claim Amendments, 20 December 2002

1. (twice amended) A composition comprising a plurality of recombinant nucleocapsid protein monomers, the primary sequences of which are derived from duck hepatitis B virus, wherein at least a first portion of said monomers includes at least one non-HBV hapten, and wherein said monomers may be assembled to form a particle antigenic with respect to said hapten [wherein said plurality of monomers are assembled to form a particle].

3. (amended) The composition of claim 1 [2] wherein at least a second portion of said nucleocapsid protein monomers includes a second non-HBV hapten different from said first hapten.

10. (amended) The composition of claim 1 [2] wherein said first hapten is associated with a disease condition caused by an agent selected from the group consisting of: single stranded DNA viruses, double stranded DNA viruses, single stranded RNA viruses, double stranded RNA viruses, intracellular parasites, fungi, bacteria, and cancer.

24. (twice amended) A composition comprising

recombinant duck HBcAg; and,

a non-HBV hapten, said hapten being linked to said duck HBcAg;

wherein said recombinant duck HBcAg is capable of disassembly and reassembly into a particle.